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Multilayer pharmaceutical form with a matrix which influences the delivery of a modulatory substance

The invention relates to a multilayer pharmaceutical form with a matrix which influences the delivery of a modulatory substance.

Prior art

EP-A 0 463 877 describes pharmaceutical compositions with delayed active ingredient release consisting of a core with an active pharmaceutical ingredient as a monolayer coating film which comprises a water-repellent salt and a water-insoluble copolymer of ethyl acrylate, methyl methacrylate and trimethylammonium-ethyl methacrylate chloride. The water-repellent salt may be for example Ca stearate or Mg stearate. Sigmoidal release plots are obtained.

EP-A 0 225 085, EP-A 0 122 077 and EP-A 0 123 470 describe the use of organic acid in medicament cores which are provided with various coatings from organic solutions. Essentially sigmoidal release characteristics result.

EP-A 0 436 370 describes pharmaceutical compositions with delayed active ingredient release consisting of a core with an active pharmaceutical ingredient and an organic acid and an outer coating film which has been applied by aqueous spraying and is a copolymer of ethyl acrylate, methyl methacrylate and trimethylammonium-ethyl methacrylate chloride. In this case, sigmoidal release plots are likewise obtained.

WO 00/19984 describes a pharmaceutical preparation consisting of (a) a core comprising an active ingredient, where appropriate a carrier and conventional pharmaceutical additives, and the salt of an organic acid whose proportion in the weight of the

core amounts to 2.5 to 97.5% by weight, and (b) an outer coating film which consists of one or more (meth)acrylate copolymers and, where appropriate, of conventional pharmaceutical excipients, where 40 to 100% by weight of the (meth)acrylate copolymers consist of 93 to 98% by weight of free-radical polymerized C_1 to C_4 alkyl esters of acrylic or methacrylic acid and 7 to 2% by weight of (meth)acrylate monomers with a quaternary ammonium group in the alkyl radical and may where appropriate be present in a mixture, with 1 to 60% by weight of one or more further (meth)acrylate copolymers which are different from the first-mentioned (meth)acrylate copolymers and are composed of 85 to 100% by weight of free-radical polymerized C_1 to C_4 alkyl esters of acrylic or methacrylic acid and, where appropriate, up to 15% by weight of further (meth)acrylate monomers with basic groups or acidic group in the alkyl radical.

WO 00/74655 describes an active ingredient release system with a double release pulse which is brought about by a three-layer structure. The core comprises an active ingredient and a substance which swells in the presence of water, e.g. a crosslinked polyacrylic acid. An inner coating consists of a water-insoluble carrier material, e.g. a cationic (meth)acrylate copolymer, and comprises a water-soluble particulate material, e.g. a pectin, whereby pore formation can be achieved. An outer coating comprises the same or a different active ingredient. In the gastrointestinal tract there is initial release of the active ingredient located on the outside, while the active ingredient present in the core is released after a time lag through the pores in the middle layer. The three-layer pharmaceutical form may optionally also have a further coating, e.g. composed of a carboxyl group-containing (meth)acrylate copolymer.

US 5,508,040 describes a multiparticulate pharmaceutical form consisting of large number of pellets which are held together in a binder. The pellets have an active ingredient and an osmotically active modulator, e.g. NaCl or an organic acid, in the core. The pellet cores are provided with coatings of different thicknesses, e.g. composed of (meth)acrylate copolymers with quaternary ammonium groups. To reduce the permeability, the coatings also comprise hydrophobic substances, e.g. fatty acids, in amounts of 25% by weight or above. The multiparticulate pharmaceutical form is released through a the contained active ingredient in a large number of pulses which corresponds to the number of pellet populations with coatings of different thicknesses.

EP 1 064 938 A1 describes a pharmaceutical form which has an active ingredient and a surface-active substance (surfactant) in the core. The core may additionally comprise an organic acid and is coated with (meth)acrylate copolymers with quaternary ammonium groups. "Pulsatile" release plots are obtained. Stepped release plots can be obtained by combining pellets with different coatings in one pharmaceutical form.

WO 01/13895 describes bimodal release systems for active ingredients having a sedative hypnotic effect. The release profiles are achieved by mixtures of different pellet populations.

WO 01/37815 describes multilayer release systems for controlled, pulsatile delivery of active ingredients. In this case, an inner membrane which can be dissolved by the active ingredient formulation present in the cores is present. Also present is an outer membrane which additionally has a pore-forming substance.

WO 01/58433 describes multilayer release systems for controlled, pulsatile delivery of active ingredients.

In this case, the active ingredient is present in the core and is surrounded by a polymer membrane which is soluble in intestinal juice. An outer membrane consists of a mixture of a polymer which is soluble in intestinal juice with a water-insoluble polymer in defined ranges of amounts. An intermediate layer comprising an organic acid may be present between the inner and outer membrane.

Problem and solution

Starting from EP-A 0 436 370 and WO 00/19984, it was intended to develop a pharmaceutical form which permits the permeability of film coatings to be influenced by intrinsic modulation so that release profiles with zero order, first order, first order with initial accelerated phase, slow-fast, fast-slow profiles can be adjusted individually depending on the active ingredient and therapeutic requirements.

The problem is solved by a

multilayer pharmaceutical form for controlled active ingredient release, essentially comprising

a) optionally a neutral core (nonpareilles),
b) an inner controlling layer comprising a substance having a modulating effect, which is embedded in a matrix which influences the delivery of the modulatory substance and which comprises pharmaceutically usable polymers, waxes, resins and/or proteins, and where appropriate an active ingredient,
c) an active ingredient layer comprising an active pharmaceutical ingredient and, where appropriate, a substance having a modulating effect,
d) an outer controlling layer comprising at least 60% by weight of one or a mixture of a plurality of (meth)acrylate copolymers composed of 98 to 85 C_1 to C_4 alkyl esters of (meth)acrylic acid and 2 to 15% by weight of methacrylate monomers with a quaternary ammonium group in the alkyl radical, and, where appropriate, up to 40% by weight of further pharmaceutically usable polymers,

where the layers may additionally and in a manner known per se comprise pharmaceutically usual excipients.

Implementation of the invention

The invention relates to a multilayer pharmaceutical form for controlled active ingredient release comprising essentially an optional core a) and layers b), c) and d). It is also possible in addition for usual topcoat layers, which may for example be pigmented, to be present.

Optional core a)

A neutral core (nonpareilles) may be present.

The inner controlling layer b)

The inner controlling layer comprises a substance having a modulating effect, which is embedded in a matrix which influences the delivery of the modulatory substance and which comprises pharmaceutically usable polymers, waxes, resins and/or proteins or consists thereof, and additionally may comprise where appropriate an active ingredient. To assist the formulation it is possible to admix further pharmaceutically customary excipients such as, for example, binders such as cellulose and derivatives thereof, plasticizers, polyvinylpyrrolidone (PVP), humectants, disintegration promoters, lubricants, disintegrants, starch and derivatives thereof, sugars and/or solubilizers.

Suitable processes for producing the inner controlling layer b) are direct compression, compression of dry, wet or sintered granules, extrusion and subsequent rounding off, wet or dry granulation or direct pelleting (e.g. on plates) or, if an optional core a) is present, by binding powders (powder layering) onto active ingredient-free cores (nonpareilles).

The inner controlling layer b) influences the delivery

of the substance having a modulating effect and of the active ingredient which is present where appropriate from the core layer. The inner controlling layer consists of pharmaceutically usable polymers, waxes, proteins and/or other pharmaceutically customary excipients.

Examples of suitable polymers are the following:

copolymers of methyl methacrylate and/or ethyl acrylate and methacrylic acid, copolymers of methyl methacrylate, methyl acrylate and methacrylic acid, copolymers of methyl methacrylate, butyl methacrylate and dimethylethyl methacrylate, copolymers of methyl methacrylate, ethyl acrylate and trimethylammoniumethyl methacrylate, copolymers of methyl methacrylate and ethyl acrylate, copolymers of ethyl acrylate, methyl acrylate, butyl methacrylate and methacrylic acid,

polyvinylpyrolidones (PVPs), polyvinyl alcohols, polyvinyl alcohol-polyethylene glycol graft copolymer (Kollicoat®), starch and derivatives thereof, polyvinyl acetate phthalate (PVAP, Coateric®), polyvinyl acetate (PVAc, Kollicoat), vinyl acetate/vinylpyrolidone copolymer (Kollidon® VA64), vinyl acetate: crotonic acid 9:1 copolymer (VAC: CRA, Kollicoat® VAC), polyethylene glycols with a molecular weight above 1000 (g/mol) and/or shellac,

celluloses such as, for example, anionic carboxymethyl-cellulose and salts thereof (CMC, Na-CMC, Ca-CMC, Blanose, Tylopur), carboxymethylethylcellulose (CMEC, Duodcell®), hydroxyethylcellulose (HEC, Klucel), hydroxypropylcellulose (HPC), hydroxypropylmethyl-cellulose (HPMC, Pharmacoat, Methocel, Sepifilm, Viscontran, Opadry), hydroxymethylethylcellulose (HEMC), ethylcellulose (EC, Ethocel®, Aquacoat®, Surelease®), methylcellulose (MC, Viscontran, Tylopur, Methocel), cellulose esters, cellulose glycolate,

cellulose acetate phthalate (CAP, Cellulosi acetas, PhEur, cellulose acetate phthalate, NF, Aquateric®), cellulose acetate succinate (CAS), cellulose acetate trimeliate (CAT), hydroxypropylmethylcellulose phthalate (HPMCP, HP50, HP55), hydroxypropylmethyl-cellulose acetate succinate (HPMCAS-LF, -MF, -HF).

The inner controlling layer b) may preferably consist of a polymer or contain one which is insoluble in water or only swellable in water.

The inner controlling layer may consist of a wax such as, for example, carnauba wax and/or beeswax, or comprise the latter.

The inner controlling layer may comprise the resin shellac or consist thereof.

The inner controlling layer may comprise a protein such as, for example, albumin, gelatin, zein, gluten, collagen and/or lectins, or consist thereof. The protein of the inner controlling layer should preferably have no therapeutic function, as is the case with protein or peptide active ingredients, so that the technical effects of the active ingredient layer c) on the one hand and of the inner controlling layer b), if the latter comprises an active ingredient, on the other hand do not overlap where possible.

Substances having a modulating effect

Substances having a modulating effect which are to be used according to the invention may have a molecular weight of below 500, be in solid form and be ionic.

The substance having a modulating effect is preferably water-soluble.

The substance having a modulating effect may be for

example an organic acid or the salt of an organic or inorganic acid.

The substance having a modulating effect may be for example succinic acid, citric acid, tartaric acid, laurylsulphuric acid, a salt of these acids or a salt of the following anions: taurochlolate and other cholates, chlorides, acetates, lactates, phosphates and/or sulphates.

Mode of functioning of the components with one another

The mode of functioning of the substance having a modulating effect in the multilayer pharmaceutical form can be described approximately as follows:
Na succinate (succinic acid), Na acetate and citric acid increase the rate of active ingredient delivery.
NaCl and Na citrate decrease the rate of active ingredient delivery.

If the active ingredient layer c) comprises in addition to the inner core layer a) a substance having a modulating effect, the active ingredient delivery is determined firstly by the substance having a modulating effect which is present in the outer layer, the active ingredient layer c). If this substance is substantially consumed, the effect of the substance having a modulating effect in the inner layer, the inner controlling layer b), starts and determines further active ingredient release.

The various active ingredient delivery profiles can be adapted to the active ingredient and the therapeutic aim by combining different amounts of one and/or different substances having a modulating effect in the two layers. There is in addition the effect of the matrix itself which in turn itself controls delivery of the substance having a modulating effect.

The amount of active ingredient delivered is essentially controlled by the outer controlling layer d). If the inner controlling layer additionally comprises an active ingredient, this layer can be used to adjust the active ingredient delivery profile towards the end of active ingredient delivery.

If the active ingredients themselves comprise ionic groups or are present in the salt form, the active ingredient itself can influence the effect of the substance or substances having a modulating effect so that the latter is diminished or enhanced. This interaction can be utilized as further control element.

The active ingredient layer c)

The active ingredient layer c) comprises an active pharmaceutical ingredient, and where appropriate a substance having a modulating effect, which may be identical to or different from the substance having a modulating effect of the core layer.

Active ingredients

The multilayer pharmaceutical form of the invention is suitable in principle for any active ingredients. Medicinal substances in use can be found in reference works such as, for example, the Rote Liste or the Merck Index.

The active ingredients or medicinal substances employed for the purposes of the invention are intended to be used on or in the human or animal body in order

1. to cure, to alleviate, to prevent or to diagnose disorders, conditions, physical damage or pathological symptoms.
2. to reveal the condition, the status or the functions of the body or mental states.
3. to replace active substances or body fluids

produced by the human or animal body.

4. to ward off, to eliminate or to render harmless pathogens, parasites or exogenous substances, or
5. to influence the condition, the status or the functions of the body or mental states.

These pharmaceutically active substances may belong to one or more active ingredient classes such as ACE inhibitors, adrenergics, adrenocorticosteroids, acne therapeutic agents, aldose reductase inhibitors, aldosterone antagonists, alpha-glucosidase inhibitors, alpha 1 antagonists, remedies for alcohol abuse, amino acids, amoebicides, anabolics, analeptics, anaesthetic additions, anaesthetics (non-inhalational), anaesthetics (local), analgesics, androgens, angina therapeutic agents, antagonists, antiallergics, antiallergics such as PDE inhibitors, antiallergics for asthma treatment, further antiallergics (e.g. leukotriene antagonists, antianaemics, antiandrogens, antianxiolytics, antiarthritics, antiarrhythmics, antiatheriosclerotics, antibiotics, anticholinergics, anticonvulsants, antidepressants, antidiabetics, antidiarrhoeals, antidiuretics, antidotes, antiemetics, antiepileptics, antifibrinolytics, antiepileptics, antihelmintics, antihistamines, antihypotensives, antihypertensives, antihypertensives, antihypotensives, anticoagulants, antimycotics, antiestrogens, antiestrogens (non-steroidal), antiparkinson agents, antiinflammatory agents, antiproliferative active ingredients, antiprotozoal active ingredients, antirheumatics, antischistosomicides, antispasmolytics, antithrombotics, antitussives, appetite suppressants, arteriosclerosis remedies, bacteriostatics, beta-blockers, beta-receptor blockers, bronchodilators, carbonic anhydrase inhibitors, chemotherapeutic agents, choleretics, cholinergics, cholinergic agonists, cholinesterase inhibitors, agents for the treatment of ulcerative colitis, cyclooxygenaze inhibitors diuretics, ectoparasiticides, emetics, enzymes, enzyme

inhibitors, enzyme inhibitors, active ingredients to counter vomiting, fibrinolytics, fungistatics, gout remedies, glaucoma therapeutic agents, glucocorticoids, glucocorticosteroids, haemostatics, cardiac glycosides, histamine H2 antagonists, hormones and their inhibitors, immunotherapeutic agents, cardiotonics, coccidiostats, laxatives, lipid-lowering agents, gastrointestinal therapeutic agents, malaria therapeutic agents, migraine remedies, microbiocides, Crohn's disease, metastasis inhibitors, migraine remedies, mineral preparations, motility-increasing active ingredients, muscle relaxants, neuroleptics, active ingredients for treatment of estrogens, osteoporosis, otologicals, antiparkinson agents, phytopharmaceuticals, proton pump inhibitors, prostaglandins, active ingredients for treating benign prostate hyperblasia, active ingredients for treating pruritus, psoriasis active ingredients, psychoactive drugs, free-radical scavengers, renin antagonists, thyroid therapeutic agents, active ingredients for treating seborrhoea, active ingredients to counter seasickness, spasmolytics, alpha- and beta-sympathomimetics, platelet aggregation inhibitors, tranquilizers, ulcer therapeutic agents, further ulcer therapeutic agents, agents for the treatment of urolithiasis, virustatics, vitamins, cytokines, active ingredients for combination therapy with cytostatics, cytostatics.

Active ingredients

Examples of suitable active ingredients are acarbose, acetylsalicylic acid, abacavir, aceclofenac, aclarubicin, acyclovir, actinomycin, adalimumab, adefovir, adefovirdipivoxil, adenosylmethionine, adrenaline and adrenaline derivatives, agalsidase alpha, agalsidase beta, alemtuzumab, almotriptan, alphacept, allopurinol, almotriptan, alosetron, alprostadil, amantadine, ambroxol, amisulpride,

amlodipine, amoxicillin, 5-aminosalicylic acid, amitriptyline, amlodipine, amoxicillin, amprenavir, anakinra, anastrozole, androgen and androgen derivatives, apomorphine, aripiprazole, arsenic trioxide, artemether, atenolol, atorvastatin, atosiban, azathioprine, azelaic acid, barbituric acid derivatives, balsalazide, basiliximab, beclapermin, beclomethasone, bemiparin, benzodiazepines, betahistine, bexaroten, bezafibrate, bicalutamide, bimatoprost, bosentan, botulinus toxim, brimonidine, brinzolamide, budesonide, budipine, bufexamac, bumetanide, buprenorphine, bupropion, butizine, calcitonin, calcium antagonists, calcium salts, candesartan, capecitabine, captopril, carbamazepine, carifenacin, carvedilol, caspofungin, cefaclor, cefadroxil, cefalexin cefalosporins, cefditoren, cefprozil, celecoxib, cepecitabine, cerivastatim, cetirizine, cetrorelix, cetuximab, chenodeoxycholic acid, chorionic gonadotropin, ciclosporin, cidofovir, cimetidine, ciprofloxacin, cisplatin, cladribine, clarithromycin, clavulanic acid, clindamycin, clobutinol, clonidine, clopidogrel, codeine, caffeine, colestyramine, cromoglicic acid, cotrimoxazole, coumarin and coumarin derivatives, darbepoetin, cysteamine, cysteine, cytarabine, cyclophosphamide, cyproterone, cytarabine, daclizumab, dalfopristin, danaparoid, dapiprazole, darbepoetin, defepripone, desipramine, desirudin, desloaratadine, desmopressin, desogestrel, desonide, dexibuprofen, dexketoprofen, disoproxil, diazepam and diazepam derivatives, dihydralazine, diltiazem, dimenhydrinate, dimethyl sulphoxide, dimeticon, dipivoxil, dipyridarnoi, dolasetron, domperidone, and domperidane derivatives, donepzil, dopamine, doxazosin, doxorubizin, doxylamine, diclofenac, divalproex, dronabinol, drospirenone, drotrecogin alpha, dutasteride, ebastine, econazole, efavirenz, eletripan, emidastine, emtricitabine, enalapril, encepur, entacapone, enfurvirtide, ephedrine, epinephrine, eplerenone, epoetin and epoetin

derivatives, eprosartan, eptifibatide, ertapenem, esomeprazole, estrogen and estrogen derivatives, etanercept, ethenzamide, ethinestradiol, etofenamate, etofibrate, etofylline, etonogestrel, etoposide, exemestan, exetimib, famciclovir, famotidine, faropenan daloxate, felodipine, fenofibrate, fentanyl, fenticonazole, fexofenadine, finasteride, fluconazole, fludarabine, flunarizine, fluorouracil, fluoxetine, flurbiprofen, flupirtine, flutamide, fluvastatin, follitropin, fomivirsen, fondaparinux, formoterol, fosfomicin, frovatriptan, furosemide, fusidic acid, gadobenate, galantamine, gallopamil, ganciclovir, ganirelix, gatifloxacin, gefitinib, gemfibrozil, gentamicin, gepirone, progestogen and progestogen derivatives, ginkgo, glatiramer, glibenclamide, glipizide, glucagon, glucitol and glucitol derivatives, glucosamine and glucosamine derivatives, glycoside antibiotics, glutathione, glycerol and glycerol derivatives, hypothalamus hormones, goserelin, grepafloxacin, gyrase inhibitors, guanethidine, gyrase inhibitors, haemin, halofantrine, haloperidol, urea derivatives as oral antidiabetics, heparin and heparin derivatives, cardiac glycosides, hyaluronic acid, hydralazine, hydrochlorothiazide and hydrochlorothiazide derivatives, hydroxyomeprazole, hydroxyzine, ibritumomab, ibuprofen, idarubicin, ifliximab, ifosfamide, iloprost, imatinib, imidapril, imiglucerase, imipramine, imiquimod, imidapril, indometacin, indoramine, infliximab, insulin, insulin glargin, interferons, irbesartan, irinotecan, isoconazole, isoprenaline, itraconazole, ivabradines, iodine and iodine derivatives, St. John's wort, potassium salts, ketoconazole, ketoprofen, ketotifen, lacidipine, lansoprazole, laronidase, latanoprost, leflunomide, lepirudin, lercanidipine, leteprinim, letrozole, levacetylmethadol, levetiracetam, levocetirizine, levodopa, levodrpropicin, levomethadone, licofelone, linezolide, lipinavir, lipoic acid and lipoic acid derivatives, lisinopril,

lisuride, lofepramine, lodoxamide, lomefloxacin, lomustine, loperamide, lopinavir, loratadine, lornoxicam, losartan, lumefantrine, lutropine, magnesium salts, macrolide antibiotics, mangafodipir, maprotiline, mebendazole, mebeverine, meclozine, mefenamic acid, mefloquine, meloxicam, memantine, mepindolol, meprobamate, meropenem, mesalazine, mesuximide, metamizole, metformin, methadone, methotrexate, methyl 5-amino-4-oxopentanoate, methylnaloxone, methylnaloxone, methylnaltrexones, methylphenidate, methylprednisolone, metixen, metoclopramide, metoprolol, metronidazole, mianserin, mibefradil, miconazole, mifepristone, miglitol, miglustad, minocycline, minoxidil, misoprostol, mitomycin, mizolastine, modafinil, moexipril, montelukast, moroctocog, morphinans, morphine and morphine derivatives, moxifloxacin, ergot alkaloids, nalbuphine, naloxone, naproxen, naratriptan, narcotine, natamycin, nateglinide, nebivolol, nefazodone, nelfinavir, neostigmine, neramexan, nevirapine, nicergoline, nicethamide, nifedipine, niflumic acid, nimodipine, nimorazole, nimustine, nesiritide, nisoldipine, norfloxacin, novamine sulphone, noscapine, nystatin, ofloxacin, oktotride, olanzapine, olmesartan, olsalazine, oseltamivir, omeprazole, omoconazole, ondansetron, orlistat, oseltamivir, oxaceprol, oxacillin, oxaliplatin, oxaprozin, oxcarbacepin, oxicodone, oxiconazole, oxymetazoline, palivizumab, palanosetron, pantoprazole, paracetamol, parecoxib, paroxetine, pegaspargase, peginterferon, pegfilgrastrim, penciclovir, oral penicillins, pentazocine, pentifylline, pentoxifylline, peptide antibiotics, perindopril, perphenazine, pethidine, plant extracts, phenazone, pheniramine, phenylbutyric acid, phenytoin, phenothiazines, phenserine, phenylbutazone, phenytoin, pimecrolimus, pimozide, pindolol, pioglitazone, piperazine, piracetam, pirenzepine, piribedil, pirlindol, piroxicam, pramipexol, pramlintide, pravastatin, prazosin,

procaine, promazine, propiverine, propranolol, propionic acid derivatives, propyphenazone, prostaglandins, protionamide, proxyphylline, quetiapine, quinapril, quinaprilate, quinupristine, ramipril, ranitidine, rabeprazole, raloxifen, ranolazine, rasburicase, reboxetin, repaclinides, reproterol, reserpine, revofloxacin, ribavirin, rifampicin, riluzoles, rimexolone, risedronate, risperidone, ritonavir, rituximab, rivastimen, risatriptan, rofecoxib, ropinirol, ropivacaine, rosiglitazone, roxatidine, roxithromycin, ruscogenin, rosuvastatin, rutoside and rutoside derivatives, sabadilla, salbutamol, salicylates, salmeterol, saperconazoles, thyroid hormones, scopolamine, selegiline, sertaconazole, sertindole, sertraline, sevelamer, sibutramine, sildenafil, silicates, simvastatin, sirolimus, sitosterol, sotalol, spaglumic acid, sparfloxacin, spectinomycin, spiramycin, spirapril, spironolactone, stavudine, streptomycin, sucralfate, sufentanil, sulbactam, sulphonamides, sulphasalazine, sulpiride, sultamicillin, sultiam, sumatriptan, suxamethonium chloride, tacrine, tacrolimus, tadalafil, taliolol, talsaclidine, tamoxifen, tasonermin, tazarotene, tegafur, tegaserod, telithromycin, telmisartan, temoporfin, temozolomide, tenatoprazole, tenecteplase, teniposide, tenofovir, tenoxicam, teriparatide, terazosin, terbinafine, terbutaline, terfenadine, teriparatide, terlipressin, tertatolol, testosterone and testosterone derivatives, tetracyclines, tetryzoline, tezosentan, theobromine, theophylline, theophylline derivatives, thiamazole, thiotepa, thr. growth factors, tiagabine, tiapride, tibolone, ticlopidine, tilidine, timolol, tinidazole, tioconazole, tioguanine, tiotropium, tioxolone, tirazetam, tiropramide, trofiban, tizanidine, tolazoline, tolbutamide, tolcapone, tolnaftate, tolperisone, tolterodine, topiramate, topotecan, torasemide, tramadol, tramazoline, trandolapril, tranylcypromine, trapidil, trastuzumab, travoprost,

trazodone, trepostinil, triamcinolone and triamcinolone derivatives, triamterene, trifluperidol, trifluridine, trimetazidines, trimethoprim, trimipramine, tripelennamine, triprolidine, trifosfamide, tromantadine, trometamol, tropalpine, trovafloxacin, troxerutin, tulobuterol, trypsins, tyramine, tyrothricin, urapidil, ursodeoxycholic acid, theophylline ursodeoxycholic acid, valaciclovir, valdecoxib, valganciclovir, valproic acid, valsartan, vancomycin, vardenafil, vecuronium chloride, venlafaxine, verapamil, verteporfin, vidarabine, vigabatrine, viloxazine, vinblastine, vincamine, vincristine, vindesine, vinorelbine, vinpocetine, viquidil, vitamin D and derivatives of vitamin D, voriconazole, warfarin, xantinol nicotinate, ximelagatran, xipamide, zafirlukast, zalcitabine, zaleplon, zanamivir, zidovudine, ziprasidone, zoledronic acid, zolmitriptan, zolpidem, zoplicone, zotepine and the like.

The active ingredients can if desired also be used in the form of their pharmaceutically acceptable salts or derivatives, and in the case of chiral active ingredients it is possible to employ both optically active isomers and racemates or mixtures of diastereomers. If desired, the compositions of the invention may also comprise two or more active pharmaceutical ingredients.

The outer controlling layer d)

The outer controlling layer d) comprises at least 60, preferably at least 80, particularly preferably 90 to 100, % by weight of one or a mixture of a plurality of (meth)acrylate copolymers composed of 98 to 85 C_1 to C_4 alkyl esters of (meth)acrylic acid and 2 to 15% by weight of methacrylate monomers with a quaternary ammonium group in the alkyl radical, and, where appropriate, up to 40, preferably up to 20, in particular 0 to 10, % by weight of further pharmaceutically usable polymers. However, is particularly preferred for no further pharmaceutically usable polymers to be present. The data on the % by weight of the abovementioned polymers in the outer controlling layer d) are moreover calculated without taking account of any pharmaceutically usual excipients which are additionally present.

Appropriate (meth)acrylate copolymers are disclosed for example in EP-A 181 515 or DE patent 1 617 751. They are polymers which are soluble or swellable irrespective of the pH and are suitable for medicament coatings. A possible production process to be mentioned is bulk polymerization in the presence of an initiator which forms free radicals and is dissolved in the monomer mixture. The polymer can likewise be produced by means of solution or precipitation polymerization. The polymer can be obtained in this way in the form of a fine powder, achievable in the case of bulk polymerization by grinding and in the case of solution and precipitation polymerization for example by spray drying.

The (meth)acrylate copolymer is composed of 85 to 98% by weight of free-radical polymerized C_1 to C_4 alkyl esters of acrylic or methacrylic acid and 15 to 2% by weight of (meth)acrylate monomers with a quaternary ammonium group in the alkyl radical.

Preferred C_1 to C_4 alkyl esters of acrylic or methacrylic acid are methyl acrylate, ethyl acrylate, butyl acrylate, butyl methacrylate and methyl methacrylate.

The particularly preferred (meth)acrylate monomer with quaternary ammonium groups is 2-trimethylammoniumethyl methacrylate chloride.

An appropriate copolymer may be composed for example of 50-70% by weight of methyl methacrylate, 20-40% by weight of ethyl acrylate and 7-2% by weight of 2-trimethylammoniumethyl methacrylate chloride.

A specifically suitable copolymer comprises 65% by weight of methyl methacrylate, 30% by weight of ethyl acrylate and 5% by weight of 2-trimethylammoniumethyl methacrylate chloride be composed (EUDRAGIT® RS).

A further suitable (meth)acrylate copolymer may be composed for example of 85 to less than 93% by weight of C_1 to C_4 alkyl esters of acrylic or methacrylic acid and more than 7 to 15% by weight of (meth)acrylate monomers with a quaternary ammonium group in the alkyl radical. Such (meth)acrylate monomers are commercially available and have long been used for release-slowing coatings.

A specifically suitable copolymer comprises for example 60% by weight of methyl methacrylate, 30% by weight of ethyl acrylate and 10% by weight of 2-trimethyl-ammoniumethyl methacrylate chloride (EUDRAGIT® RL).

It is possible where appropriate for up to 40, preferably up to 20, in particular 0 to 10, % by weight of further pharmaceutically usable polymers to be present in the outer controlling layer d).
Examples of suitable polymers are:

copolymers of methyl methacrylate and/or ethyl acrylate and methacrylic acid, copolymers of methyl methacrylate, methyl acrylate and methacrylic acid, copolymers of methyl methacrylate, butyl methacrylate and dimethylethyl methacrylate, copolymers of methyl methacrylate, ethyl acrylate and trimethylammoniumethyl methacrylate, copolymers of methyl methacrylate and ethyl acrylate, copolymers of ethyl acrylate, methyl acrylate, butyl methacrylate and methacrylic acid,

polyvinylpyrolidones (PVPs), polyvinyl alcohols, polyvinyl alcohol-polyethylene glycol graft copolymer (Kollicoat®), starch and derivatives thereof, polyvinyl acetate phthalate (PVAP, Coateric®), polyvinyl acetate (PVAc, Kollicoat), vinyl acetate/vinylpyrolidone copolymer (Kollidone® VA64), vinyl acetate: crotonic acid 9:1 copolymer (VAC: CRA, Kollicoat® VAC), polyethylene glycols with a molecular weight above 1000 (g/mol), chitosan, a (meth)acrylate copolymer consisting of 20-40% by weight of methyl methacrylate and 60 to 80% by weight of methacrylic acid, a crosslinked and/or uncrosslinked polyacrylic acid, an Na alginate, and/or a pectin,

celluloses such as, for example, anionic carboxymethylcellulose and salts thereof (CMC, Na-CMC, Ca-CMC, Blanose, Tylopur), carboxymethylethylcellulose (CMEC, Duodcell®), hydroxyethylcellulose (HEC, Klucel), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC, Pharmacoat, Methocel, Sepifilm, Viscontran, Opadry), hydroxymethylethylcellulose (HEMC), ethylcellulose (EC, Ethocel®, Aquacoat®, Surelease®), methylcellulose (MC, Viscontran, Tylopur, Methocel), cellulose esters, cellulose glycolate, cellulose acetate phthalate (CAP, Cellulosi acetas, PhEur, cellulose acetate phthalate, NF, Aquateric®), cellulose acetate succinate (CAS), cellulose acetate trimeliate (CAT), hydroxypropylmethylcellulose phtha-

late (HPMCP, HP50, HP55), hydroxypropylmethylcellulose acetate succinate (HPMCAS-LF, -MF, -HF).

Layer thicknesses and proportions by weight

Optional core a)

If neutral cores (nonpareilles) are used as carriers, they may be in the range of an average diameter of about 50 to 1500 µm.

Inner controlling layer b)

The inner controlling layer comprises

a) a substance having a modulating effect,
b) pharmaceutically usable polymers, waxes, resins and/or proteins,
c) optionally an active ingredient

b) can amount in relation to a) to 50 to 400, preferably 10 to 200, % by weight.
c) can be present in relation to a) and b) in amounts of 10 to 100% by weight.

Active ingredient layer c)

The active ingredient layer c) may account for 10 to 400, preferably 50 to 200, % by weight based on the core layer a) and the inner controlling layer b).

Outer controlling layer d)

The outer controlling layer d) may have a proportion by weight of from 2.5 to 100, preferably 10 to 70, particularly preferably 20 to 60, % by weight based on the core layer a), the inner controlling layer b) and the active ingredient layer c). The layer thickness is about 4 to 150, in particular 15 to 75, particularly preferably 30 to 70, µm.

Excipients customary in pharmacy

Layers a), b), c) and d) may additionally and in a manner known per se comprise excipients customary in pharmacy.

Excipients customary in pharmacy, occasionally also referred to as customary additives, are added to the formulation of the invention, preferably during production of the granules or powders. It is, of course, always necessary for all the substances employed to be toxicologically acceptable and usable in particular in medicaments without a risk for patients.

The amounts employed and the use of excipients customary in pharmacy for medicament coatings or layerings are familiar to the skilled worker. Examples of possible excipients or additives customary in pharmacy are release agents, pigments, stabilizers, antioxidants, pore formers, penetration promoters, gloss agents, aromatizing substances or flavourings. They serve as processing aids and are intended to ensure a reliable and reproducible production process and good long-term storage stability or they achieve additional advantageous properties in the pharmaceutical form. They are added to the polymer preparations before processing and may influence the permeability of the coatings, it being possible to utilize this where appropriate as additional control parameter.

Release agents:

Release agents usually have lipophilic properties and are usually added to the spray suspensions. They prevent agglomeration of the cores during the film coating. Talc, Mg stearate or Ca stearate, ground silica, kaolin or nonionic emulsifiers with an HLB of between 3 and 8 are preferably employed. The usual amounts employed of release agent are between 0.5 to

100% by weight based on the weight of the cores.

Pigments:

Pigments incompatible with the coating agent are in particular those pigments which, if added directly to the (meth)acrylate copolymer dispersion, e.g. by stirring in, in the usual amounts used of, for example, 20 to 400% by weight based on the dry weight of the (meth)acrylate copolymer, lead to destabilization of the dispersion, coagulation, to signs of inhomogeneity or similarly unwanted effects. The pigments to be used are moreover of course non-toxic and suitable for pharmaceutical purposes. Concerning this, see also, for example: Deutsche Forschungsgemeinschaft, *Farbstoffe für Lebensmittel*, Harald, Boldt Verlag KG, Boppard (1978); Deutsche Lebensmittelrundschau 74, No. 4, p. 156 (1978); Arzneimittelfarbstoffverordnung AmFarbV of 25.08.1980.

Pigments incompatible with the coating agent may be for example alumina pigments. Examples of incompatible pigments are orange yellow, cochineal red lake, coloured pigments based on alumina or azo dyes, sulphonic acid dyes, orange yellow S (E110, C.I. 15985, FD&C Yellow 6), indigo carmine (E132, C.I. 73015, FD&C Blue 2), tartrazine (E 102, C.I. 19140, FD&C Yellow 5), Ponceau 4R (E 125, C.I. 16255, FD&C Cochineal Red A), quinoline yellow (E 104, C.I. 47005, FD&C Yellow 10), erythrosine (E127, C.I. 45430, FD&C Red 3), azorubine (E 122, C.I. 14720, FD&C Carmoisine), amaranth (E 123, C.I. 16185, FD&C Red 2), acid brilliant green (E 142, C.I. 44090, FD&C Green S).

The E numbers indicated for the pigments relate to an EU numbering. Concerning this, see also "Deutsche Forschungsgemeinschaft, Farbstoffe für Lebensmittel, Harald Boldt Verlag KG, Boppard (1978); Deutsche Lebensmittelrundschau 74, No. 4, p. 156 (1978); Arzneimittelfarbstoffverordnung AmFarbV of 25.08.1980.

The FD&C numbers relate to the approval in food, drugs and cosmetics by the U.S. food and drug administration (FDA) described in: U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Cosmetics and Colors: Code of Federal Regulations - Title 21 Color Additive Regulations Part 82, Listing of Certified Provisionally Listed Colors and Specifications (CFR 21 Part 82).

Plasticizers

Further additives may also be plasticizers. The usual amounts are between 0 and 50, preferably 5 to 20, % by weight based for example on the (meth)acrylate copolymer of the outer layer d).

Plasticizers may influence the functionality of the polymer layer, depending on the type (lipophilic or hydrophilic) and added amount. Plasticizers achieve through physical interaction with the polymers a reduction in the glass transition temperature and promote film formation, depending on the added amount. Suitable substances usually have a molecular weight of between 100 and 20 000 and comprise one or more hydrophilic groups in the molecule, e.g. hydroxyl, ester or amino groups.

Examples of suitable plasticizers are alkyl citrates, glycerol esters, alkyl phthalates, alkyl sebacates, sucrose esters, sorbitan esters, diethyl sebacate, dibutyl sebacate and polyethylene glycols 200 to 12 000. Preferred plasticizers are triethyl citrate (TEC), acetyl triethyl citrate (ATEC) and dibutyl sebacate (DBS). Mention should additionally be made of esters which are usually liquid at room temperature, such as citrates, phthalates, sebacates or castor oil. Esters of citric acid and sebacic acid are preferably used.

Addition of the plasticizers to the formulation can be

carried out in a known manner, directly, in aqueous solution or after thermal pretreatment of the mixture. It is also possible to employ mixtures of plasticizers.

Processes for producing a multilayer pharmaceutical form

The multilayer pharmaceutical form can be produced in a manner known per se by means of usual pharmaceutical processes such as direct compression, compression of dry, wet or sintered granules, extrusion and subsequent rounding off, wet or dry granulation or direct pelleting (e.g. on plates) or by binding of powders (powder layering) onto active ingredient-free beads or cores (nonpareilles) or active ingredient-containing particles, by means of spray processes or fluidized bed granulation. Application of the outer controlling layer d) can take place by means of known and usual processes such as, for example, spray application of polymer solutions or polymer dispersions.

Possible release characteristics

The multilayer pharmaceutical form is particularly suitable for achieving specific active ingredient release characteristics. Mention should be made of active ingredient release characteristics of zero order (linear), 1st order (accelerated), fast-slow, slow-fast release characteristics.

Dosage forms/uses

The multilayer pharmaceutical forms of the invention are initially in the form of tablets or pellets. These can in turn be used as ingredient of a multiparticulate pharmaceutical form, of pellet-containing tablets, minitablets, capsules, sachets, effervescent tablets or powders for reconstitution. It is possible according to the invention for multiparticulate pharmaceutical forms

also to include in particular mixtures of formulated pellets comprising different active ingredients. A further possibility is for multiparticulate pharmaceutical forms of the invention to comprise pellet populations which are loaded with one and the same active ingredient but are differently formulated and show different release profiles. It is possible in this way for mixed release profiles of one or more active ingredients to be achieved and for a more refined adaptation for the desired therapy to be carried out via the mixtures.

EXAMPLES

EUDRAGIT® RS = copolymer of 65% by weight of methyl methacrylate, 30% by weight of ethyl acrylate and 5% by weight of 2-trimethylammoniumethyl methacrylate chloride, 30% dispersion; EUDRAGIT® RS 30D = 30% dispersion;
EUDRAGIT® RS PO = product in powder form;
EUDRAGIT® NE 30D = copolymer of 50% by weight of methyl methacrylate and 50% by weight of ethyl acrylate.

Examples 1-5 (not according to the invention)

In order to examine the influence of various substances having a modulating effect on the outer controlling layer d), pellets without a matrix which influences the delivery of the substance having a modulating effect were produced. Pellets without a substance having a modulating effect but with microcrystalline cellulose (Example 5) were used for comparison. It is possible in this way to ascertain effects such as an accelerated or a slowed active ingredient delivery irrespective of matrix.

A mixture of 1290 g of theophylline powder, 65 g of Kollidon 25 and 6.5 g of Aerosil 200 are sprinkled onto

700 g of core material in a coating pan and bound to the core material by simultaneous spraying of a solution of 33 g of theophylline and 10 of Kollidon 25 in 500 g of demineralized water. A spray suspension of 400 g of EUDRAGIT® RS 30 D (corresponding to 120 g of polymer), 60 g of talc, 24 g of triethyl citrate, 0.6 g of yellow iron oxide and 538.3 g of demineralized water is applied in a fluidized bed system to 600 g of the theophylline pellets produced in this way with non-slow-release modulator core. The applied amount of polymer thus corresponds to 20% of the starting material.

The pellets produced in Example 1-5 were investigated for active ingredient delivery in a PhEur phosphate buffer of pH 6.8 in a USP dissolution tester:

Example	1	2	3	4	5
Core layer a)	Sodium acetate crystals	Sodium chloride crystals	Sodium succinate crystals	Citric acid crystals	Micro-crystalline cellulose granules
Inner controlling layer b)	-	-	-	-	-
Active ingredient layer c)	theophylline	theophylline	theophylline	theophylline	theophylline
Outer controlling layer d)	EUDRAGIT® RS 30 D	EUDRAGIT® RS 30 D	EUDRAGIT® RS 30 D	EUDRAGIT® RS 30 D	EUDRAGIT® RS 30 D
Time [h]					
0	0	0	0	0	0
0.5	3.1	0.4	7.0	6.3	1.8
1	5.4	1.1	13.2	10.2	3.0
2	9.2	2.1	28.2	18.1	5.2
4	14.8	3.9	65.9	35.1	11.6
6	20.1	5.5	77.9	51.0	20.7
8	25.0	7.1	89.7	66.8	30.9
10	29.1	8.4	96.3	80.0	42.7

The release values show the first order profile characteristic of diffusion processes. Thus, without control of modulator release, an equilibrium very quickly results in the coated pellet, which

definitively adjusts the permeability of the final coating at the start of release.

The release profile of the pellets with microcrystalline cellulose (Example 5) is between those with sodium acetate and sodium chloride. Thus, an accelerating effect results for sodium acetate, citric acid and sodium succinate, and a reducing effect results for sodium chloride.

Example 6 "linear (zero order)"

1000 g of sodium chloride are granulated in a compulsory mixer with 300 g of EUDRAGIT® NE 30 D (equivalent to 100 g of copolymer)

A mixture of 1290 g of theophylline powder, 65 g of Kollidon 25 and 6.5 g of Aerosil 200 are sprinkled onto 700 g of the cores produced in this way with slow-release modulator delivery in a coating pan and bound to the core material by simultaneous spraying of a solution of 33 g of theophylline and 10 of Kollidon 25 in 500 g of demineralized water.

A spray suspension of 400 g of EUDRAGIT® RS 30 D (corresponding to 120 g of polymer), 60 g of talc, 24 g of triethyl citrate, 0.6 g of yellow iron oxide and 538.3 g of demineralized water is applied to 600 g of the theophylline pellets produced in this way with slow-release modulator core in a fluidized bed system. The release plot shows a 0 order profile, i.e. it is virtually linear.

Example 7 "fast/slow"

500 g of sodium chloride are mixed in a compulsory mixer with 500 g of EUDRAGIT® RS PO (copolymer powder) and, after addition of 100 g of triethyl citrate, melt granulated at a temperature of 70°C.

A mixture of 1100 g of theophylline powder, 190 g of sodium succinate, 65 g of Kollidon 25 and 6.5 g of Aerosil 200 are sprinkled onto 700 g of the cores produced in this way with slowed modulator delivery in a coating pan and bound to the core material by simultaneous spraying of a solution of 33 g of theophylline and 10 of Kollidon 25 in 500 g of demineralized water.

A spray suspension of 400 g of EUDRAGIT® RS 30 D (corresponding to 120 g of polymer), 60 g of talc, 24 g of triethyl citrate, 0.6 g of yellow iron oxide and 538.3 g of demineralized water was applied to 600 g of theophylline pellets produced in this way with slow-release modulator core in a fluidized bed system. The applied amount of polymer thus corresponds to 20% of the starting material.

There is very fast linear delivery of about 40% of the active ingredient within a period of 2 hours. Release then suddenly becomes slower and distinctly delayed, with the remaining 60% of active ingredient undergoing linear delivery over a period of 10 hours.

Example 8 "slow/fast"

200 g of glycerol monostearate and 300 g of carnauba wax are melted at 70°C. 250 g of sodium acetate are mixed therewith. This melt is applied to 700 g of neutral pellets (nonpareilles) by conventional melt-coating process in a fluidized bed system.

A mixture of 1100 g of theophylline powder, 190 g of sodium chloride, 65 g of Kollidon 25 and 6.5 g of Aerosil 200 are sprinkled onto 700 g of the cores produced in this way with slowed modulator delivery in a coating pan and bound to the core material by simultaneous spraying of a solution of 10 of Kollidon 25 in 500 g of demineralized water.

A spray suspension of 400 g of EUDRAGIT® RS 30 D (corresponding to 120 g of polymer), 60 g of talc, 24 g of triethyl citrate, 0.6 g of yellow iron oxide and 538.3 g of demineralized water was applied to 600 g of theophylline pellets produced in this way with slow-release modulator core in a fluidized bed system. The applied amount of polymer thus corresponds to 20% of the starting material.

There is very slow linear delivery of about 20% of the active ingredient within a period of 4 hours. Release then suddenly becomes faster, with the remaining 80% of active ingredient undergoing linear delivery over a period of 6 hours.

Example 9 "accelerated"

500 g of sodium acetate are mixed in a compulsory mixer with 500 g of EUDRAGIT® RS PO and 500 g of theophylline powder and, after addition of 100 g of triethyl citrate, melt granulated at a temperature of 70°C.

A mixture of 760 g of theophylline powder, 560 g of sodium chloride, 65 g of Kollidon 25 and 6.5 g of Aerosil 200 are sprinkled onto 700 g of the cores produced in this way with slowed modulator delivery/active ingredient delivery in a coating pan and bound to the core material by simultaneous spraying of a solution of 10 of Kollidon 25 in 500 g of demineralized water.

A spray suspension of 400 g of EUDRAGIT® RS 30 D (corresponding to 120 g of polymer), 60 g of talc, 24 g of triethyl citrate, 0.6 g of yellow iron oxide and 538.3 g of demineralized water was applied to 600 g of theophylline pellets produced in this way with slow-release modulator core in a fluidized bed system. The applied amount of polymer thus corresponds to 20% of the starting material.

The active ingredient is released within a period of 10 hours, with the initial release being very small. A continuous large acceleration in release is to be observed over the investigated period.

Overview of Examples 6 to 9

	Example 6 *"linear"*	***Example 7*** *"fast/slow"*	***Example 8*** *"slow/fast"*	***Example 9*** *"accelerated"*
Neutral core layer a)	-	-	nonpareilles	-
Inner controlling layer b) Modulator Matrix Active ingredient	 NaCl EUDRAGIT® NE -	 NaCl EUDRAGIT® NE -	 Na acetate Carnauba wax -	 Na acetate EUDRAGIT® RS Theophylline
Active ingredient layer c) Active ingredient Modulator	 Theo-phylline -	 Theo-phylline Na succinate	 Theophylline NaCl	 Theophylline NaCl
Outer controlling layer d)	EUDRAGIT® RS			

EUDRAGIT® RS = copolymer of 65% by weight methyl methacrylate, 30% by weight ethyl acrylate and 5% by weight 2-trimethylammonium ethyl methacrylate chloride.

EUDRAGIT® NE = copolymer of 50% by weight methyl methacrylate and 50% by weight ethyl acrylate.